

Review Article

Major haemorrhage: past, present and future

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Summary

Major haemorrhage is a leading cause of morbidity and mortality worldwide. Successful treatment requires early recognition, planned responses, readily available resources (such as blood products) and rapid access to surgery or interventional radiology. Major haemorrhage is often accompanied by volume loss, haemodilution, acidaemia, hypothermia and coagulopathy (factor consumption and fibrinolysis). Management of major haemorrhage over the past decade has evolved to now deliver a 'package' of haemostatic resuscitation including: surgical or radiological control of bleeding; regular monitoring of haemostasis; advanced critical care support; and avoidance of the lethal triad of hypothermia, acidaemia and coagulopathy. Recent trial data advocate for a more personalised approach depending on the clinical scenario. Fresh frozen plasma should be given as early as possible in major trauma in a 1:1 ratio with red blood cells until the results of coagulation tests are available. Tranexamic acid is a cheap, life-saving drug and is advocated in major trauma, postpartum haemorrhage and surgery, but not in patients with gastrointestinal bleeding. Fibrinogen levels should be maintained $> 2 \text{ g.l}^{-1}$ in postpartum haemorrhage and $> 1.5 \text{ g.l}^{-1}$ in other haemorrhage. Improving outcomes after major traumatic haemorrhage is now driving research to include extending blood-product resuscitation into prehospital care.

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Introduction

A person dies from injury nearly every 3 min, and 40% of these deaths are due to major haemorrhage or its consequences [1]. Death from haemorrhage is early, with up to 60% of deaths occurring within the first 3 h of injury [2]. Haemorrhage continues to be the leading cause of maternal death globally [3]. Causes of haemorrhage may also vary geographically. In high-resource settings, the most common indications for massive transfusion are major surgery (61.2%) followed by trauma (15.4%), whereas obstetric bleeding only constitutes 1.8% of cases [4].

Since the publication of major haemorrhage guidelines from the British Society of Haematology in 2015 and Association of Anaesthetists in 2016, there have been numerous randomised controlled trials in this field. A summary of these trials is displayed in Table 1.

The aims of this article are to: describe the definitions of major haemorrhage; briefly recap the mechanisms and pathophysiology of bleeding; provide a contemporary narrative review of transfusion support during major haemorrhage across a range of clinical indications; and highlight ongoing trials and areas of uncertainty.



Table 1 Summary characteristics of recent randomised controlled trials in major haemorrhage.

Study setting	Patients and no. randomised	Intervention(s)	Comparator	Key findings
Pre-hospital/trauma				
Sperry et al. [5] 27 pre-hospital air medical transport, 9 USA Level 1 trauma centres	Blunt or penetrating trauma transferred to a trauma centre and at risk of haemorrhagic shock (SBP < 90 mmHg and HR > 108 beats.min ⁻¹ or SBP < 70 mmHg) n = 501	Thawed plasma – 2 units (either group AB or A with low anti-B titre (<1:100))	Goal-directed crystalloid-based resuscitation (SBP > 90 mmHg)	30-day mortality was lower in the plasma group (23% vs. 33%, –9.8% difference, 95%CI –18.6 to –1.0; p = 0.03) Median (IQR) initial prothrombin ratio was lower in the plasma group (1.2 (1.1–1.4) vs. 1.3 (1.1–1.6); p < 0.001)
Moore et al. [6] Single centre USA Level 1 trauma centre	Adult trauma patients in haemorrhagic shock (SBP ≤ 70 mmHg or 71–90 mmHg plus heart rate ≥ 108 beats.min ⁻¹) n = 144	Two units of rapidly thawed AB plasma	Saline	No difference in 28-day mortality between both study groups (15% in plasma group vs. 10% in 0.9% saline group; p = 0.37)
Crombie et al. [7] Four prehospital critical care services in the UK	Traumatic injury with hypotension (SBP < 90 mmHg) or absent palpable radial pulse secondary to haemorrhage n = 432	Two units of O negative RBCs and 2 units of lyophilised plasma (LyoPlas) Further resuscitated with saline if SBP <	Saline up to 4 × 250 ml bags	No significant difference in mortality between the two groups. 43% vs. 45% (ARR 0.97 (95%CI 0.78–1.2)) No significant difference in failure to clear lactate between the two groups: 50% vs. 55% (ARR 0.94, 95%CI 0.78–1.13)
CRASH collaborators [8] (CRASH-3) 175 hospitals in 29 countries	Adults with TBI within 3 h of injury (changed from within 8 h of injury in Sep 2016), GCS ≤ 12 or ICH on CT scan n = 12,737	Tranexamic acid 1 g over 10 min followed by intravenous infusion of 1 g over 8 h	Saline	Risk of head-injury related death in patients with mild–moderate head injury was lower in the tranexamic acid group (RR 0.78, 95%CI 0.64–0.95)
Baksaas-Asen et al. [9] 7 MTCs in Europe	Adult patients with traumatic injury and signs of bleeding requiring activation of the MHP and if RBC transfusion had been started n = 396	Transfusion guided by VHA	Transfusion guided by conventional coagulation tests	No difference in proportion of patients who were alive and free of massive transfusion at 24 h (67% vs. 64%, OR 1.15 95%CI 0.76–1.73)
Obstetrics				
WOMAN collaborators [10] 193 hospitals in 23 countries	Women aged ≥ 16 y or with a clinical diagnosis of PPH after a vaginal birth or caesarean section n = 20,060	Tranexamic acid 1 g administered intravenously over 10 min	Placebo administered intravenously over 10 min	Death due to bleeding was significantly reduced in women given tranexamic acid (155/10036 (1.5%) vs. 191/9985 (1.9%), RR 0.81; 95%CI 0.65–1.00; p = 0.045). The effect was greater if given within 3 h (RR 0.69; 95%CI 0.52–0.91; p = 0.008)
Senthiles et al. [11] 27 centres in France	≥34 weeks gestation expected to undergo caesarean before or during labour n = 4551	Tranexamic acid 1 g	Saline	Lower incidence of red cell transfusion or estimated blood loss by 2 days (556/2086 (26.7%) vs. 653/2067 (31.6%); Adjusted RR 0.84 (95%CI –0.75 to –0.93; p = 0.003)

(continued)

Table 1 (continued)

Study setting	Patients and no. randomised	Intervention(s)	Comparator	Key findings
Surgery				
Devereaux et al. [12] 114 hospitals in 22 countries	Patients undergoing non-cardiac surgery n = 9535	Tranexamic acid 1 g	Placebo	Lower incidence of composite bleeding outcome (life-threatening bleeding, major bleeding or bleeding into critical organ) in the tranexamic group (433/4757 patients (9.1%) vs. 4778 patients (11.7%); HR 0.76; 95%CI 0.67 to 0.87)
Callum et al. [13] 11 Canadian hospitals	Adult patients experiencing clinically significant bleeding and hypofibrinogenemia after cardiac surgery n = 827	Fibrinogen concentrate 4 g for each ordered dose	Cryoprecipitate 10 units for each	Fibrinogen concentrate was non-inferior to cryoprecipitate (16.3 units vs. 17.0 units, (ratio 0.96 (1-sided 97.5% CI, $-\infty$ to 1.09; $p < 0.001$ for noninferiority)
Smith et al. [14] Single centre, USA	Adult patients undergoing cardiac surgery with use of CPB n = 100	Prothrombin complex 15 IU.kg ⁻¹	FFP 10–15 ml.kg ⁻¹	Fewer patients in prothrombin complex group required RBC transfusion (7/51 (13.7%) vs. 15/49 (30.6%); $p = 0.04$), with greater improvements in PT and INR
Gastrointestinal bleeding				
Roberts et al. [15] 164 hospitals in 15 countries	Adults at risk of death from upper or lower gastrointestinal bleeding n = 12,009	1 g tranexamic loading dose followed by 3 g maintenance over 24 h	Saline	Tranexamic did not reduce the risk of death from bleeding (222/5956 (4%) vs. 226/5981 (4%), RR 0.99 95%CI 0.82–0.18) and resulted in higher rates of thromboembolic events (48/5952 (0.8%) vs. 26/5977 (0.5%), RR 1.85, 95%CI 1.15 to 2.98)

ARR, absolute risk reduction; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; HR, hazard ratio; ICH, intracranial haemorrhage; MHP, major haemorrhage protocol; PPH, postpartum haemorrhage; RBC, red blood cell; RR, relative risk; SBP, systolic blood pressure; TBI, traumatic brain injury; VHA, viscoelastic haemostatic assays.

Major haemorrhage

Definitions of major haemorrhage (in trauma) have traditionally been variable [16] and include: loss of more than one circulating blood volume within 24 h (around 70 ml.kg⁻¹, approximately 5 l in a 70 kg adult); loss of 50% of total blood volume in < 3 h; or bleeding in excess of 150 ml.min⁻¹.

Scores such as the Assessment of Blood Consumption and the shock index (heart rate divided by systolic blood pressure) are available to guide early prediction of massive transfusion but are not used routinely in clinical practice and lack high sensitivity [17]. A recent Delphi consensus identified a pragmatic transfusion-based definition for clinical research major haemorrhage – ≥ 4 units of any blood component transfused within 2 h of injury [18]. The current trend is towards a more pragmatic definition based on the clinical effect of haemorrhage on the patient's

physiology. Major haemorrhage can be considered to be bleeding which leads to a systolic blood pressure of < 90 mmHg or a heart rate of > 110 beats.min⁻¹. However, changes in physiology may be masked in certain patient groups, e.g. older patients, pregnancy and people taking beta-blockers.

Definitions may also vary between patient populations. In obstetrics, postpartum haemorrhage has been defined as blood loss > 500 ml from the genital tract within 24 h of delivery [19]. This can be further defined as minor (500–1000 ml) or major (>1000 ml). Major can be divided into moderate (1000–2000 ml) or severe (>2000 ml). In patients with upper and/or lower gastrointestinal bleeding, various risk scores have been validated to stratify severity of bleeding to guide subsequent management [20–22]. Anaesthetists encounter major haemorrhage in a wide variety of situations including: the emergency department

(trauma, upper gastrointestinal haemorrhage); elective and emergency surgery (particularly cardiac, liver, orthopaedics and vascular); obstetrics; and critical care. The general principles of management will be similar in these situations. However, these various sources of bleeding may have varying pathophysiology and so behave in different ways.

Mechanisms: a brief primer

The four main causes of major haemorrhage are trauma; surgery; obstetric; and medical (e.g. gastrointestinal bleeding, anticoagulants). The mechanism of major haemorrhage differs depending on the aetiology of the bleeding.

The pathophysiological effects of haemorrhage related to trauma and surgery are similar as the haemorrhage is initiated by vessel and tissue injury. Physiological haemostasis is initiated with the formation of a platelet-fibrin clot which seals and stops the bleeding [23]. Tissue injury leads to increased thrombin generation, shutdown of fibrinolysis and platelet activation, which in turn leads to increased clot formation and prevention of bleeding [24].

Trauma-induced coagulopathy occurs when the coagulation system is unable to sustain haemostasis. It is characterised by early endogenous coagulopathy mediated by activation of protein C coupled with systemic coagulopathy [1]. This is further worsened by hypothermia, hypoxia and acidaemia. Hypothermia reduces plasma coagulation enzyme activity by 10% per °C and coupling between platelet adhesion and activation is lost between 30°C and 34°C [25]. Acidaemia reduces factor complex assembly; as a result of this, enzyme activity is 50% of normal at pH 7.2, 30% at pH 7.0 and only 20% at pH 6.8 [25]. Reversal of Starling forces, thought to be due to sodium redistribution and neuroendocrine activation, leads to the shift of interstitial fluid into the vascular compartment and resuscitation with crystalloids and colloids leads to dilutional coagulopathy [24]. Even balanced resuscitation strategies that attempt to deliver functional whole blood with red cells, plasma and platelets will deliver a dilute final product due to the presence of anticoagulants and additive solutions [24]. Hormonal and cytokine changes lead to a complex cascade of events leading to disruption and degradation of the endothelial glycocalyx [26]. The glycocalyx is an important determinant of vascular permeability and contains significant concentrations of heparin-like substances (e.g. syndecan 1, thrombomodulin), that when degraded (e.g. in critical illness or trauma) may induce autoheparinisation, which in turn exacerbates coagulopathy [24–26].

Major obstetric haemorrhage can occur in the antepartum or postpartum period. Causes of antepartum

haemorrhage include: placental abruption; placenta previa; and uterine rupture. The main causes of postpartum haemorrhage are often referred to as the 4Ts: tone (uterine atony); trauma; tissue (retained placenta); or thrombin (coagulopathy) [27]. A detailed review of the haemostatic changes during pregnancy can be found elsewhere [27] but coagulopathy develops only in a minority of women with postpartum haemorrhage. However, it is difficult to predict and needs urgent identification to avoid spiralling into uncontrollable bleeding. A low fibrinogen concentration is an important predictor of severity and poor clinical outcome [28, 29]. True disseminated intravascular coagulation, albeit rare in this population, is seen with amniotic fluid embolism, severe pre-eclampsia, HELLP syndrome and severe placental abruption [27].

The main causes of upper gastrointestinal bleeding are non-variceal (e.g. peptic ulcer disease, gastritis, oesophagitis) and oesophageal varices [30]. The aetiology of peptic ulcer disease has evolved. An ageing population had led to a rise in the use of antiplatelet and non-steroidal anti-inflammatory drugs meaning *Helicobacter pylori* is no longer the leading cause. Significant bleeding results from erosion of an underlying artery. In gastritis and oesophagitis, mucosal abrasions lead to bleeding. Oesophageal varices develop as a shunt between the portal system and systemic circulation. As the pressure in this system increases, variceal rupture occurs, leading to bleeding. The most common cause of lower gastrointestinal bleeding is diverticular disease [22]. The extent of the bleeding depends on the size of the vessel/diverticulum. In all these causes, as bleeding progresses, consumptive and dilutional coagulopathy occurs resulting in major haemorrhage.

Transfusion support during major haemorrhage

All staff involved in caring for patients who are likely to experience major haemorrhage should be appropriately trained to recognise and manage blood loss and be familiar with their hospital's local major haemorrhage protocol. A summary of the 2022 British Society of Haematology guidelines for the haematological management of major haemorrhage are shown in Table 2.

The aims of transfusion support (haemostatic resuscitation) during major haemorrhage (Fig. 1) are to: restore circulating blood volume for adequate tissue perfusion and oxygenation; maintain and regularly monitor haemostasis; and avoid the triad of hypothermia, acidaemia and coagulopathy.

Table 2 Summary of key recommendations from the 2022 British Society of Haematology guidelines for the haematological management of major haemorrhage.

Recommendation
General Use a transfusion threshold of 70 g.l ⁻¹ and maintain a haemoglobin concentration between 70–90 g.l ⁻¹ . A minimum RBC:FFP ratio of 2:1 should be used until the results of conventional or near-patient coagulation tests are available. Once laboratory results are available, further FFP should be administered to maintain a prothrombin ratio of < 1.5-times normal. Haemostasis testing (conventional coagulation tests or VHAs) should be performed every 30–60 min. Fibrinogen supplementation should be given if fibrinogen concentration < 1.5 g.l ⁻¹ . Platelet count should be maintained above 50 × 10 ⁹ .l ⁻¹ during active bleeding.
Major trauma Plasma should be given as early as possible in a 1:1 (and not > 1:2) ratio with RBCs until coagulation results are available. Tranexamic acid should be given, including in those patients with mild–moderate TBI, as soon as possible after the injury and no later than 3 h. Common prescription is a 1 g intravenous bolus over 10 min followed by 1 g infusion over 8 h.
Obstetrics/postpartum haemorrhage General recommendations (described above) for RBC transfusion and plasma apply. Fibrinogen supplementation should be given if fibrinogen concentrations < 2.0 g.l ⁻¹ . An initial dose of tranexamic (1 g intravenously) should be given to women with PPH within 3 h of bleed onset. If bleeding continues after 30 min, or it stopped and restarted within 24 h of the first tranexamic dose, a second dose of 1 g should be given.
Gastrointestinal bleeding Tranexamic acid is not recommended for patients with acute gastrointestinal bleeding. Consider the limited role of coagulation tests as predictors of bleeding in patients with liver disease. Excessive plasma transfusions may raise portal venous pressures in patients with variceal disease.
Surgery Patients undergoing major non-cardiac surgery and at-risk of major bleeding and/or transfusion should receive 1 g of tranexamic prior to skin incision.
Organisational Major haemorrhage protocols should be reviewed annually, or whenever there are changes in guidance or new evidence becomes available to suggest change in practice. Robust patient and sample identification systems for unknown patients are essential to avoid errors in emergency and multiple casualty situations. All patients receiving a blood transfusion must wear a patient identification wristband containing the unique identifier. If a patient's blood group is unknown or unsure, universal components or appropriate substitutes should be used to avoid delays in issuing blood during major bleeding.

FFP, fresh frozen plasma; PPH, postpartum haemorrhage; TBI, traumatic brain injury; VHA, viscoelastic haemostatic assays.

Red blood cells

Red blood cell (RBC) transfusion is indicated when 30–40% of circulating blood volume is lost (approximately 1500 ml in a 70 kg male, female equivalents are unknown) and is immediately required if more than 40% of blood volume is lost (1500–2000 ml). Red blood cell transfusion aims to improve oxygen delivery and recent guidelines recommend a target haemoglobin (Hb) concentration of 70–90 g.l⁻¹ [31]. Haemoglobin concentration is routinely used to guide transfusion; however, limitations in its interpretation include the confounding effects of resuscitation measures such as intravenous fluids. It is important to realise that initial Hb measurements (before fluid resuscitation) may be normal and not accurately reflect blood loss. This is also because patients lose whole blood and compensatory mechanisms that shift interstitial fluid take time (up to 1 h). In such cases, physiologic transfusion triggers such as haemodynamic compromise, ECG changes and acidaemia may be useful [32]. In particular, lactate and/or base deficit are sensitive tests to estimate and monitor the severity of bleeding [33, 34].

Red blood cells should be transfused through a warming device to minimise the risk of the patient developing hypothermia and rapid infuser devices may be required in life-threatening bleeding. For immediate transfusion, group O RBCs should be issued after samples have been obtained for group and crossmatch. Group O Rhesus negative and Kell negative should be prioritised for females of childbearing potential.

Fresh frozen plasma

Fresh frozen plasma (FFP) is the component of choice for treating generalised coagulopathy (often defined by abnormalities of standard coagulation tests, such as prothrombin time). It provides a balanced source of pro- and anticoagulant factors, and also contains acute phase reactants, immunoglobulin and albumin. It can also be used as a resuscitation fluid for volume expansion. Experimental studies demonstrate a beneficial role of FFP on endothelial function by maintaining glycocalyx integrity and attenuating endotoxin upregulation [35]. A therapeutic dose of 15–

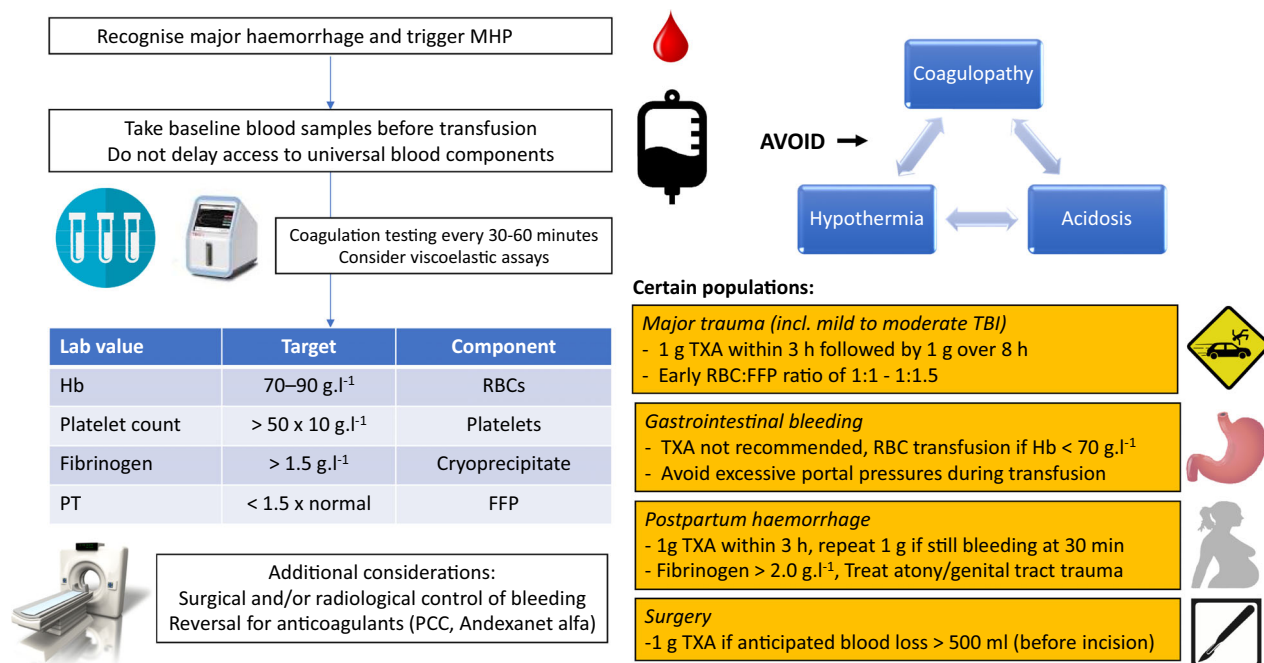


Figure 1 Key principles for the management of major haemorrhage in general, and across different clinical situations. MHP, major haemorrhage protocol; Hb, haemoglobin; RBC, red blood cell; PT, prothrombin time; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; TBI, traumatic brain injury; TXA, tranexamic acid.

20 ml.kg⁻¹ is typically recommended [36] and the approximate volume per unit of FFP is 200–275 ml.

What is the optimal RBC:FFP transfusion ratio?

In the absence of any coagulation tests being available, empiric ratio-based resuscitation is now advocated by many major haemorrhage protocols. A low ratio is pragmatically defined as 2 units of RBC for every 1 unit of FFP (2:1). Observational studies in military settings demonstrated improved survival in patients who received higher ratios [37, 38], but survivor bias [39] is a major confounder in these studies. This is a time-dependent bias that occurs where patients who live longer are more likely to receive a treatment than patients who die early.

In 2015, Holco et al. carried out a landmark trial which allocated randomly 680 severely injured patients who arrived at trauma centres in North America to early administration of plasma, platelets and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio. The authors found no difference in overall survival (the primary outcome). Death due to exsanguination was lower in the 1:1:1 (high ratio) group. More patients in the 1:1:1 group achieved anatomic haemostasis in the operating theatre; defined as an objective assessment by the surgeon indicating that bleeding in the

surgical field was controlled and no further haemostatic interventions were necessary [40]. However, for all 23 prespecified complications (including sepsis, transfusion-related complication, acute respiratory distress syndrome and venous thromboembolism), no differences were seen between these two groups at 30 days post-randomisation.

Clinicians have raised concerns regarding the implementation of these high ratios in yet-to-be-studied, non-trauma patient populations where the underlying pathophysiology may be different. For example, in obstetrics, the most common causes of haemorrhage are uterine atony and genital tract trauma. These are not associated with significant coagulopathy, and fibrinogen levels are relatively well maintained even with large blood losses [41]. One observational study found no difference in 30-day survival in patients without traumatic injury who required a massive transfusion and received a high RBC:FFP ratio compared with those who received a low ratio [42]. Another meta-analysis, mainly based on observational studies, found that the highest survival benefit was at a RBC:FFP ratio of 1.5:1 in trauma and non-trauma settings [43]. Taken together, these data highlight the need for further studies to refine major haemorrhage protocols in non-trauma populations.

The findings of the trial by Holcomb et al. led to trials evaluating the efficacy and safety of prehospital plasma in

trauma patients. The underlying rationale was that intervening close to the time of injury may reduce the downstream complications of coagulopathy and shock. A prehospital air medical plasma trial showed that thawed plasma was safe and resulted in a reduction in 30-day mortality [5]. However, Moore et al. in a trial investigating major bleeding after trauma found no difference in 28-day mortality when prehospital plasma was given [6]. More recently, Crombie et al. investigated the role of prehospital RBC transfusion and lyophilised plasma but found no evidence of an effect on mortality or lactate clearance [7]. Closer inspection of the trials suggests that the difference in mortality rates may be due to longer transport times and different modes of transport. Transport times were longer in the trial by Sperry et al. (39–52 min) compared with the trial by Moore et al. (16–28 min) and Crombie et al. (approximately 20 min). Participants in that trial were also older and more severely injured [7].

Platelets

Platelet dysfunction is seen during major trauma and shock, and may be associated with increased mortality, even when the platelet count is within the normal reference range [44]. Significant thrombocytopenia is considered a late event in major haemorrhage [36]. Current guidelines recommend maintaining a platelet count $> 50 \times 10^9 \text{ l}^{-1}$ in major haemorrhage but higher counts ($> 100 \times 10^9 \text{ l}^{-1}$) may be required in patients with traumatic brain injury or intracranial haemorrhage [45].

Of increasing interest is the management of patients who are taking antiplatelet drugs and present with major bleeding. Baharoglu et al. allocated randomly patients with supratentorial intracranial haemorrhage, who were on an antiplatelet medication for at least 7 days before injury and who had a GCS > 8 , to receive standard care or standard care with platelet transfusion within 90 min of diagnostic brain imaging [46]. Platelet transfusion was associated with an increased risk of death or dependence in patients receiving antiplatelet therapy and presenting with an acute intracranial haemorrhage. Most patients in this trial were taking aspirin (a cyclo-oxygenase inhibitor) and therefore it is unclear whether the findings are generalisable to the increasing numbers of patients who are now taking adenosine diphosphate receptor antagonists such as clopidogrel. Observational data show that the use of platelet transfusions in patients with gastrointestinal bleeding, who are taking antiplatelet medications and without thrombocytopenia, may increase mortality without any effect on rebleeding rates [47]. Further research is needed into the optimal use of platelet transfusions.

Fibrinogen

Fibrinogen is crucial for clot formation and haemostasis but precise levels for fibrinogen repletion (therapeutically or for prophylaxis) in specific patient populations remain to be fully defined [48]. In obstetrics, a fibrinogen concentration $< 2 \text{ g l}^{-1}$ has a 100% positive predictive value for progression from moderate to severe haemorrhage [19]. Two therapeutic options for concentrated fibrinogen are available to supplement fibrinogen: cryoprecipitate and fibrinogen concentrate. Cryoprecipitate is the principal source of fibrinogen concentrate in the UK. There has been considerable interest in fibrinogen concentrate due to its potential advantages such as reduced infection risk (cryoprecipitate in non-purified and one pool is obtained from five donors; fibrinogen concentrate is purified and pathogen-reduced) and delivery of a standardised concentration of fibrinogen. However, clinical evidence of superiority of fibrinogen concentrates over cryoprecipitate is currently lacking. A recent trial found that fibrinogen concentrate was non-inferior to cryoprecipitate in patients who developed clinically significant bleeding and hypofibrinogenaemia after cardiac bypass [13]. Current guidelines recommend maintaining fibrinogen concentration $> 1.5 \text{ g l}^{-1}$ in major haemorrhage, except in obstetric haemorrhage where concentrations $> 2 \text{ g l}^{-1}$ should be targeted [36, 45].

Pharmacological interventions that may prevent or reverse coagulopathy

Tranexamic acid

The evidence for the efficacy and safety of tranexamic acid appears to be greater than that of many other patient blood management interventions [49]. Large, pragmatic randomised controlled trials have shown a reduction in mortality in major trauma [50], postpartum haemorrhage [10, 51] and mild-to-moderate traumatic brain injury [8], along with reducing transfusion requirements after cardiac surgery [52] and caesarean delivery [11]. More recently, Devereaux et al. [12] showed that administration of tranexamic acid results in fewer bleeding episodes (life-threatening, major or in a critical organ) when compared with placebo in a trial of 9535 patients undergoing major, non-cardiac surgery.

In patients who have suffered major trauma, tranexamic acid should be given as early as possible and ideally within the first 3 h, as the survival benefit decreases by 10% for every 15-min delay after this time-point [53]. Similar benefits of giving tranexamic acid within 3 h have also been observed in postpartum haemorrhage [10, 51]. The safety of tranexamic acid is supported by a meta-analysis of 216 trials (125,550 participants) which found no evidence of an

increased risk of thromboembolic events, myocardial infarction and cerebral ischaemia [54]. One patient group where tranexamic acid may not be beneficial is in those with gastrointestinal bleeding, where the results of a large, pragmatic trial showed no reduction in mortality and increased risk of venous thrombosis [15]. Possible reasons for these findings include the high dose of tranexamic acid that was administered (4 g over 24 h) and the delayed presentation to hospital of many of these patients, missing the early period of excessive fibrinolysis.

Current areas of tranexamic acid research include dose, route (e.g. intramuscular which may allow for quicker pre-hospital administration [55]) and timing of tranexamic acid administration across a range of clinical settings [56, 57]. A pharmacokinetic study found that in high-risk patients undergoing caesarean delivery, plasma tranexamic acid levels correlated inversely with BMI, which raises the question as to whether higher doses may be required in patients with increased BMI [58].

Prothrombin complex concentrate

Prothrombin complex concentrate is a plasma-derived concentrate containing three or four of the vitamin K-dependent coagulation factors (II, VII, IX, X) [59]. It is recommended for the rapid reversal of warfarin in the context of major or life-threatening bleeding at a starting dose of 25 IU.kg⁻¹, but there is limited evidence for its use outside this setting. Prothrombin complex concentrate has been used off-label for bleeding secondary to direct oral anticoagulants, before specific reversal drugs became available. However, it does not directly inhibit the direct oral anticoagulant or affect factor Xa levels [60].

Considering potential advantages such as faster administration, higher concentration of clotting factors and smaller infusion volumes, prothrombin complex concentrate use is being investigated in patients who are undergoing cardiac surgery (where bleeding is common, and patients may be susceptible to volume overload). Two recent small studies in cardiac surgery comparing prothrombin complex concentrates with FFP reported no safety concerns, superior haemostatic efficacy and fewer transfusion requirements with prothrombin complex concentrates [14, 61].

Aprotinin, desmopressin, recombinant activated factor VII, direct oral anticoagulant antidotes

There is currently insufficient high-quality evidence to recommend the use of any of these drugs in major bleeding.

Following re-evaluation, aprotinin can be used for the prevention of bleeding in patients at high risk of major blood loss undergoing isolated coronary artery bypass graft surgery [62]. Desmopressin has been considered as an alternative to platelet transfusions and current data, largely in the peri-operative setting, demonstrate a small reduction in transfusion requirements and blood loss of little clinical significance [63].

Use of the recombinant factor VIII in major haemorrhage has mainly been 'off-label' and systematic reviews demonstrate no evidence of an effect on mortality with an increased risk of arterial thrombosis [64]. Its use in patients without haemophilia should be restricted to clinical trials.

Direct oral anticoagulants can broadly be classified as factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and direct thrombin (IIa) inhibitors (dabigatran). There are two specific drugs approved for the reversal of direct oral anticoagulants: idarucizumab for reversal of dabigatran; and andexanet alfa for rivaroxaban and apixaban [65]. There is no currently approved reversal drug for edoxaban. Idarucizumab is a humanised monoclonal antigen binding fragment that binds dabigatran with 350 times more avidity than thrombin. Andexanet alfa is a truncated form of enzymatically inactive factor Xa. It binds and sequesters factor Xa inhibitor molecules and rapidly reduces anti-FXa activity. A detailed review of the use of these drugs can be found elsewhere [65].

Non-pharmacological strategies

Taking a good history is important to establish whether a patient is taking anticoagulants or antiplatelet drugs, as mortality from bleeding is high in these patients. Early identification will also allow for more targeted management (e.g. prothrombin complex concentrates, specific antidotes for direct oral anticoagulants). Hypothermia and hypocalcaemia should also be avoided.

The role of cell salvage is established in major, elective surgery. Implementing a cell salvage service for major haemorrhage to cover emergencies usually requires a 24-h service, with the associated costs of running such a service. A cost-effectiveness analysis of a randomised controlled trial of cell salvage use in caesarean delivery found that whilst it was marginally more effective than standard care in avoiding a blood transfusion, it was more costly with the average cost per patient estimated at £1327 (\$1542, €1545) [66]. Available evidence suggests that cell salvage may reduce transfusion requirements in emergency trauma surgery, but this does not translate to improvements in mortality or cost savings [67].

Laboratory monitoring: conventional coagulation tests vs. viscoelastic haemostatic assays

Major haemorrhage guidelines recommend performing coagulation tests and platelet counts every 30–60 min, depending on the severity of blood loss and/or until bleeding stops [36]. Key limitations of these tests include long turnaround times and poor prediction for major bleeding [9]. As a result, there has been considerable interest in the use of viscoelastic haemostatic assays which include thromboelastography, rotational thromboelastometry and

Sonoclot. A detailed review on how these devices work can be found elsewhere [9]. Perceived advantages of viscoelastic haemostatic assays include a rapid turnaround time and set of parameters that assess a global functional coagulation profile. Disadvantages include the need for a trained user to be present, poor standardisation (apart from the manufacturers' reported reference ranges) and lack of universal algorithms across specialties.

Current British Society of Haematology guidelines recommend the use of viscoelastic haemostatic assays in cardiac and liver surgery, and cautiously suggest that they

Table 3 Summary of ongoing trials. Details are given by population (P), intervention (I), comparator (C) and outcome measure (O).

Study name and trial registration	Study details and planned sample size (n)
Pre-hospital administration of lyophilised plasma for post-traumatic coagulopathy treatment (PREHO-PLYO) NCT0273812 Multicentre RCT, France	P: Adults with haemorrhagic shock of traumatic origin with SBP < 70 mmHg or shock index > 1.1 I: French lyophilised plasma C: Saline O: INR at hospital admission n = 140
Study of whole blood in frontline trauma Multicentre RCT, UK	P: Adults with traumatic major haemorrhage I: Whole blood C: Usual care (including RBCs and plasma) O: n = 850
Evaluation of a transfusion therapy using whole blood in the management of coagulopathy in Patients with Acute Traumatic Haemorrhage (T-STORHM) NCT04431999 Multicentre RCT, France	P: Severe trauma patients requiring initiation of a massive transfusion protocol I: Whole blood units for first and second MHPs C: Usual care (MHP) O: Non-inferiority on the correction of coagulopathy (as determined by MA on TEG) n = 200
Chilled platelet study (CHIPS) NCT04834414 Multicentre RCT, USA	P: Age 28–55 y scheduled to undergo complex cardiac surgery requiring CPB I: Cold stored platelets (1–6°C) C: Room temperature platelets O: Haemostatic efficacy determined by a modified peri-operative bleeding score n = 1000
Factor In the initial resuscitation of severe trauma-2 patients (FiiRST-2) NCT04534751 Multicentre RCT, Canada	P: Severely injured trauma patients triggering MHP within first hour of arrival to ED I: Fibrinogen concentrate 4 g and PCC 2000 IU in first and second haemorrhage packs C: Standard FFP resuscitation O: Total number of allogeneic blood products n = 350
Early cryoprecipitate in major trauma haemorrhage: CRYOSTAT-2 ISRCTN14998314 Multicentre RCT, UK	P: Adult trauma patients requiring activation of local MHP I: Early cryoprecipitate (3 pools) as soon as possible, within 90 min of admission C: Usual care according to local MHP O: 28-day all-cause mortality n = 1604

CPB, cardiopulmonary bypass; ED, emergency department; FFP, Fresh frozen plasma; MA, maximum amplitude; MHP, major haemorrhage protocol; PCC, prothrombin complex concentrate; RBC, red blood cell; RCT, randomised controlled trial; SBP, systolic blood pressure; TEG, thromboelastogram.

may also be used as part of a locally agreed algorithm to manage obstetric and trauma haemorrhage, with appropriate policies in place to maintain these devices [36, 68]. Single-centre, randomised controlled trials in trauma haemorrhage have shown reductions in mortality and clinically-relevant bleeding using viscoelastic haemostatic assays [69]. However, Baksaas-Aasen et al. compared standard major haemorrhage protocols using conventional coagulation tests with viscoelastic haemostatic assay-guided algorithms and found no difference in the primary outcome of patients who were alive and free of massive transfusion at 24 h [70].

Whichever method used (conventional tests or viscoelastic haemostatic assays), what is perhaps more important is the process of repeated testing, with comparisons and re-assessments made between longitudinal tests, rather than the results of standalone tests to guide decision-making. An important point to note with viscoelastic haemostatic assays is that they are less sensitive to detecting fibrinolysis in trauma and therefore should not be used to withhold the use of tranexamic acid.

Directions for future research

Major bleeding is a medical emergency but how can we best keep patients alive until definitive surgical or radiological interventions to control bleeding are performed? In addition, have we evaluated the full health economic implications of different strategies? The estimated cost of treating a major haemorrhage patient is £20,600 (\$23,941, €23,992) (£24,000 [\$27,862, €27,952] for massive haemorrhage [71]). Extrapolating these costs nationally gives an estimated cost of £85 million (\$99 million, €99 million) annually for managing major haemorrhage after trauma.

Haemostatic resuscitation forms the basis of initial organ support, and the type, composition and amount of which blood components are given has been the subject of intense research, yet uncertainties remain. We now have clinical trials, such as that by Sperry et al. [5], which suggest that a relatively small volume of plasma given in the pre-hospital setting may improve outcomes, but this has not been replicated in other studies. Differences in transport times have been identified as a potential reason for these findings. Such trials are pointing the way towards a level of research scrutiny which is clearly needed.

Other trials have demonstrated unexpected findings. The effect of a high-dose 24-h infusion of tranexamic acid in patients with acute gastrointestinal bleeding [15] found evidence of harm and no reduction in death due to bleeding. This result was different to the trials by Shakur et al. [50] and the WOMAN collaborators [10]. Yet, these

trials have been funded as separate standalone studies, which are expensive and resource intensive, and typically only answer only one research question at a time. Ongoing trials evaluating the role of whole blood and early fibrinogen replacement in major trauma, and cold stored platelets in surgery, will inform future practice (Table 3).

Moving forward, what is needed? Clinical trials continue to be needed, which are more efficient in design, aim to recruit the broadest range of patients and can test multiple different interventions as demonstrated in recent platform trials [72]. Trauma is increasingly recognised as a disorder of all ages, including older patients. The physiology of ageing and different responses to fluid and transfusion therapies means that future trials need to look beyond the typical young motorcyclist involved in a road traffic collision, and address outcomes in the older populations, including the increasing number of patients taking antiplatelet and anticoagulant medication. In particular, there is uncertainty on the role of platelet transfusions after head injury and traumatic intracranial haemorrhage in patients on antiplatelet medications [73]. But above all, we need to better understand how to target our different therapies by cause of bleeding. We have invested more in clinical research in trauma than other clinical settings of major bleeding, such as surgery, postpartum haemorrhage and gastrointestinal bleeding. Yet, these are the clinical settings of emergencies in which massive haemorrhage protocols are increasingly activated in our hospitals.

Whilst the focus of research so far has been on reducing early mortality, a relatively unexplored area is the long-term outcomes of patients who survive a major haemorrhage. One study reported unfavourable neurological outcomes and poor functional status in up to 50% of survivors up to one year after initial injury [74]. There also continue to be advances in surgical, radiological and endoscopy techniques to control bleeding, alongside intensive care support, all of which will lead to updated guidelines and reassessment of the principles of managing major haemorrhage in different clinical situations in the future.

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